

CLAIMS

1. A pharmaceutical composition comprising:
- a therapeutically effective amount of a first compound, said first compound being an estrogen agonist/antagonist; and
 - a therapeutically effective amount of a second compound, said second compound being a prostaglandin or a prostaglandin agonist/antagonist.
2. A pharmaceutical composition as recited in claim 1 additionally comprising a pharmaceutical carrier.
3. A pharmaceutical composition as recited in claim 2 wherein the estrogen agonist/antagonist is droloxifene, raloxifene, tamoxifen, 4-hydroxy-tamoxifen, *Cis*-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; (-)-*Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; *Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; *Cis*-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalene; 1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; *Cis*-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or 1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.
4. A pharmaceutical composition according to claim 3 wherein the second compound is PGD₁, PGD₂, PGE₂, PGE₁, PGF₂, PGF₂α or 3S-(3-Hydroxy-4-phenyl-butyl)-2R-[6-(1H-tetrazol-5-yl)-hexyl]-cyclopentanone.
6. A pharmaceutical composition according to claim 4 wherein the second compound is PGE₂.
7. A pharmaceutical composition according to claim 4 wherein the second compound is 3S-(3-Hydroxy-4-phenyl-butyl)-2R-[6-(2H-tetrazol-5-yl)-hexyl]-cyclopentanone.
8. A pharmaceutical composition according to claim 4 wherein the estrogen agonist/antagonist is *Cis*-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; (-)-*Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

Cis-1-[6'-pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalene;

1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

9. A pharmaceutical composition according to claim 8 wherein the second compound is PGE₂.
10. A pharmaceutical composition according to claim 8 wherein the second compound is 3S-(3-Hydroxy-4-phenyl-butyl)-2R-[6-(2H-tetrazol-5-yl)-hexyl]-cyclopentanone.
11. A method for treating a mammal having a condition which presents with low bone mass comprising administering to a mammal having a condition which presents with low bone mass

- a. a therapeutically effective amount of a first compound, said first compound being an estrogen agonist/antagonist; and
- b. a therapeutically effective amount of a second compound, said second compound being a prostaglandin or a prostaglandin agonist/antagonist.

12. A method as recited in claim 11 wherein the estrogen agonist/antagonist is droloxifene, raloxifene, tamoxifen, 4-hydroxy-tamoxifen, idoxifene, centrachroman,

Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

(-)-*Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

Cis-1-[6'-pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalene;

1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

13. A method as recited in claim 12 wherein the second compound is PGD₁, PGD₂, PGE₂, PGE₁, PGF₂, PGF₂α or 3S-(3-Hydroxy-4-phenyl-butyl)-2R-[6-(1H-tetrazol-5-yl)-hexyl]-cyclopentanone.
14. A method as recited in claim 13 wherein the estrogen agonist/antagonist is droloxifene.
16. A method as recited in claim 14 wherein the second compound is 3S-(3-Hydroxy-4-phenyl-butyl)-2R-[6-(1H-tetrazol-5-yl)-hexyl]-cyclopentanone.
17. A method as recited in claim 14 wherein the condition which presents with low bone mass is osteoporosis.
18. A method as recited in claim 13 wherein the estrogen agonist/antagonist is
Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
(-)-*Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
Cis-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalene;
1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;
Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or
1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.
19. A method as recited in claim 18 wherein the second compound is PGE₂.
20. A method as recited in claim 18 wherein the second compound is 3S-(3-Hydroxy-4-phenyl-butyl)-2R-[6-(1H-tetrazol-5-yl)-hexyl]-cyclopentanone.
21. A method as recited in claim 18 wherein the condition which presents with low bone mass is osteoporosis.
22. A method as recited in claim 14 wherein the first compound and the second compounds are administered substantially simultaneously.
23. A method as recited in claim 14 wherein the second compound is administered for a period of from about three months to about three years.
24. A method as recited in claim 23 followed by administration of the first compound for a period of from about three months to about three years without the administration of the second compound during the period of from about three months to about three years.

25. A method as recited in claim 23 followed by administration of the first compound for a period greater than about three years without the administration of the second compound during the greater than about three year period.
26. A method as recited in claim 18 wherein the first compound and the second compounds are administered substantially simultaneously.
27. A method as recited in claim 18 wherein the second compound is administered for a period of from about three months to about three years.
28. A method as recited in claim 27 followed by administration of the first compound for a period of from about three months to about three years without the administration of the second compound during the period of from about three months to about three years.
29. A method as recited in claim 27 followed by administration of the first compound for a period greater than about three years without the administration of the second compound during the greater than about three year period.
30. A method for treating mammals which present with low bone mass comprising administering to a mammal having a condition which presents with low bone mass the pharmaceutical composition of claim 1.
33. A kit containing a treatment for a condition which presents with low bone mass comprising:
 - a. a therapeutically effective amount of an estrogen agonist/antagonist and a pharmaceutically acceptable carrier in a first unit dosage form;
 - b. a therapeutically effective amount of a prostaglandin or a prostaglandin agonist/antagonist and a pharmaceutically acceptable carrier in a second unit dosage form; and
 - c. container means for containing said first and second dosage forms.
34. A pharmaceutical composition comprising:
 - a. a therapeutically effective amount of a first compound, said first compound being droloxifene, raloxifene, tamoxifen or idoxifene; and
 - b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride.
35. A pharmaceutical composition as recited in claim 34 additionally comprising a pharmaceutical carrier.
36. A method for treating a mammal having a condition which presents with low bone mass comprising administering to a mammal having a condition which presents with low bone mass
 - a. a therapeutically effective amount of a first compound, said first compound being droloxifene, raloxifene, tamoxifen or idoxifene; and

- b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride.
37. A method as recited in claim 36 wherein the condition which presents with low bone mass is osteoporosis.
38. A method as recited in claim 36 wherein the first compound and the second compounds are administered substantially simultaneously.
39. A method as recited in claim 36 wherein the second compound is administered for a period of from about three months to about three years.
40. A method as recited in claim 39 followed by administration of the first compound for a period of from about three months to about three years without the administration of the second compound during the period of from about three months to about three years.
41. A method as recited in claim 39 followed by administration of the first compound for a period greater than about three years without the administration of the second compound during the greater than about three year period.
42. A method for treating mammals which present with low bone mass comprising administering to a mammal having a condition which presents with low bone mass the pharmaceutical composition of claim 34.
45. A kit containing a treatment for a condition which presents with low bone mass comprising:
- a. a therapeutically effective amount of droloxifene, raloxifene, tamoxifen or idoxifene and a pharmaceutically acceptable carrier in a first unit dosage form;
- b. a therapeutically effective amount of a sodium fluoride and a pharmaceutically acceptable carrier in a second unit dosage form; and
- c. container means for containing said first and second dosage forms.
46. A pharmaceutical composition comprising:
- a. a therapeutically effective amount of a first compound, said first compound being
- Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
- (-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
- Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
- Cis-1-[6'-pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydro-naphthalene;

1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; and

- b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride, a parathyroid hormone, or growth hormone.
47. A pharmaceutical composition as recited in claim 46 additionally comprising a pharmaceutical carrier.
 48. A pharmaceutical composition as recited in claim 47 wherein the second compound is sodium fluoride.
 49. A pharmaceutical a composition as recited in claim 47 wherein the second compound is a parathyroid hormone.
 50. A pharmaceutical composition as recited in claim 47 wherein the second compound is growth hormone.
 52. A method for treating a mammal having a condition which presents with low bone mass comprising administering to a mammal having a condition which presents with low bone mass
 - a. a therapeutically effective amount of a first compound, said first compound being

Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

(-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

Cis-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalene;

1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; and
 - b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride, a parathyroid hormone, or growth hormone.

53. A method as recited in claim 52 wherein the second compound is sodium fluoride.
54. A method as recited in claim 52 wherein the second compound is a parathyroid hormone.
55. A method as recited in claim 52 wherein the second compound is growth hormone.
57. A method as recited in claim 52 wherein the condition which presents with low bone mass is osteoporosis.
58. A method as recited in claim 52 wherein the first compound and the second compound are administered substantially simultaneously.
59. A method as recited in claim 52 wherein the second compound is administered for a period of from about three months to about three years.
60. A method as recited in claim 59 followed by administration of the first compound for a period of from about three months to about three years without the administration of the second compound during the period of from about three months to about three years.
61. A method as recited in claim 59 followed by administration of the first compound for a period greater than about three years without the administration of the second compound during the greater than about three year period.
62. A method for treating mammals which present with low bone mass comprising administering to a mammal having a condition which presents with low bone mass the pharmaceutical composition of claim 46.
65. A kit containing a treatment for a condition which presents with low bone mass comprising:
 - a. a therapeutically effective amount of
 - Cis*-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
 - (-)-*Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
 - Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
 - Cis*-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydro-naphthalene;
 - 1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;
 - Cis*-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

- 1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline and a pharmaceutically acceptable carrier in a first unit dosage form;
- b. a therapeutically effective amount of sodium fluoride, a parathyroid hormone, or growth hormone and a pharmaceutically acceptable carrier in a second unit dosage form; and
 - c. container means for containing said first and second dosage forms.
66. The pharmaceutical composition as recited in claim 34 wherein the first compound is droloxifene.
67. The method as recited in claim 36 wherein the first compound is droloxifene.
68. The method as recited in claim 40 wherein the first compound is droloxifene.
69. The method as recited in claim 41 wherein the first compound is droloxifene.
72. The kit as recited in claim 45 wherein the first compound is droloxifene.
73. A pharmaceutical composition comprising:
- a. a therapeutically effective amount of a first compound, said first compound being raloxifene, tamoxifen or idoxifene; and
 - b. a therapeutically effective amount of a second compound, said second compound being a growth hormone.
74. A pharmaceutical composition as recited in claim 73 additionally comprising a pharmaceutical carrier.
75. A pharmaceutical composition as recited in claim 74 wherein the first compound is raloxifene.
79. A method for treating a mammal having a condition which presents with low bone mass comprising administering to a mammal having a condition which presents with low bone mass
- a. a therapeutically effective amount of a first compound, said first compound being raloxifene, tamoxifen or idoxifene; and
 - b. a therapeutically effective amount of a second compound, said second compound being growth hormone.
80. A method as recited in claim 79 wherein the first compound is raloxifene.
84. A method as recited in claim 79 wherein the condition which presents with low bone mass is osteoporosis.
85. A method as recited in claim 79 wherein the first compound and the second compound are administered substantially simultaneously.
86. A method as recited in claim 79 wherein the second compound is administered for a period of from about three months to about three years.

87. A method as recited in claim 86 followed by administration of the first compound for a period of from about three months to about three years without the administration of the second compound during the period of from about three months to about three years.
88. A method as recited in claim 86 followed by administration of the first compound for a period greater than about three years without the administration of the second compound during the greater than about three year period.
89. A method for treating mammals which present with low bone mass comprising administering to a mammal having a condition which presents with low bone mass the pharmaceutical composition of claim 73.
92. A kit containing a treatment for a condition which presents with low bone mass comprising:
 - a. a therapeutically effective amount of raloxifene, tamoxifen or idoxifene; and a pharmaceutically acceptable carrier in a first unit dosage form;
 - b. a therapeutically effective amount of growth hormone and a pharmaceutically acceptable carrier in a second unit dosage form; and
 - c. container means for containing said first and second dosage forms.
93. A combination that comprises an estrogen agonist/antagonist and a growth hormone secretagogue.
94. The combination of claim 93, wherein the growth hormone secretagogue is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide or its L-tartaric acid salt.
95. The combination of claim 93, wherein the estrogen agonist/antagonist is raloxifene or a pharmaceutically acceptable salt thereof.
96. The combination of claim 93, wherein the estrogen agonist/antagonist is (-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or a pharmaceutically acceptable salt thereof.
97. A method for treating a condition which presents with low bone mass comprising administering to a patient in need thereof a therapeutically effective amount of the combination of claim 93.
98. A method for treating a condition which presents with low bone mass comprising administering to a patient in need thereof a therapeutically effective amount of the combination of claim 94.
99. A method for treating a condition which presents with low bone mass comprising administering to a patient in need thereof a therapeutically effective amount of the combination of claim 95.

100. A method for treating a condition which presents with low bone mass comprising administering to a patient in need thereof a therapeutically effective amount of the combination of claim 96.
101. The method of claim 97 wherein the condition is osteoporosis.
102. A pharmaceutical composition comprising an estrogen agonist/antagonist, a growth hormone secretagogue, and a pharmaceutically acceptable carrier.
103. The composition of claim 102, wherein the growth hormone secretagogue is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide or its L-tartaric acid salt.
104. The composition of claim 102, wherein the estrogen agonist/antagonist is raloxifene or a pharmaceutically acceptable salt thereof.
105. The composition of claim 102, wherein the estrogen agonist/antagonist is (-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol or a pharmaceutically acceptable salt thereof.
106. A process for making a pharmaceutical composition comprising combining an estrogen agonist/antagonist, a growth hormone secretagogue, and a pharmaceutically acceptable carrier.
107. The process of claim 106, wherein the estrogen agonist/antagonist is raloxifene, (-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)]-5,6,7,8-tetrahydro-naphthalene-2-ol or a pharmaceutically acceptable salt thereof.
108. The process of claim 106, wherein the growth hormone secretagogue is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide or its L-tartaric acid salt.